system, the opioid agonist and antagonist are released from the system at substantially proportionate rates.

REMARKS

Reconsideration of this application as amended is respectfully requested. The Examiner's indication that claims 8 contains allowable subject matter is acknowledged with appreciation.

The claims are currently directed to transdermal dosage forms. Claims 37 and 40-49 are pending in the application. Claims 1-36 and 38-39 have been deleted without prejudice to pursuing the subject matter of these claims in a continuation application. New claims 40-49 have been added. Support for new claims 40-47 is found in the specification, e.g., at page 9-11 and support for new claims 48 and 49 are found, e.g., in original claims 4 and 10. It is respectfully submitted that no new matter has been added by virtue of these amendments.

I. Objections to the claims and specification

In the Office Action, the abstract was objected to for the presence of legal terminology. In response, each occurrence of "said" has been replaced with "the."

The specification was objected to for the presence of various informalities. In response, "bimodally" has been correctly spelled at page 3, line 13; "treatment" has been correctly spelled at page 3, line 27; "the" is not capitalized at page 7, line 22; "opioid" has been correctly spelled at page 8, line 18; the duplicative periods have been deleted from page 10, line 25 and page 35, line 22; and "patch" has been inserted after "transdermal" at page 16, line 34.

II. Rejections under 35 USC § 112

In the Office Action, claim 37 was rejected on the grounds of indefiniteness. In response, this claim has beem amended to recite "a" in place of "an" and the Examiner is respectfully requested to remove the rejections under 35 USC § 112.

III. Rejections under 35 USC § 103(a)

Claim 37 was rejected under 35 U.S.C. § 103(a) on the grounds of being obvious over WO 00/01377 or U.S. Patent No. 5,942,241 ("the Simon references") in view of U.S. Patent No. 5,968,547 ("the Reder reference"). The Examiner stated that "[i]t would have been obvious to one of ordinary skill in the art at the time Appicant's invention was made to administer the analgesic combination of the [Simon references] using the transdermal delivery system of [the Reder reference]."

With respect to independent claim 37, it is respectfully submitted that the Simon reference does not teach an opioid antagonist selected from the group consisting of naltrexone, diprenorphine, etorphine, dihydroetorphine, cyclazacine, levallorphan and pharmaceutically acceptable salts thereof, as recited in this claim. The Simon references are specifically directed to nalmefene, and teach away from other antagonists at page 3, lines 25-28 (of the WO publication), which states as follows:

> *The present author describes in the application for U.S. Patent No. 5,783,583 in great detail the unique characteristics common only to the opioid antagonist nalmefene, which sets nalmefene apart from other opioid antagonists such as, for example, naloxone and naltrexone.*

Combining the Simon references with the Reder reference does not provide motivation to modify the Simon formulations to include an antagonist other than nalmefene. Accordingly, the Examiner is requested to remove this rejection.

V. Conclusion

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn. It is believed that all claims are now in condition for allowance.

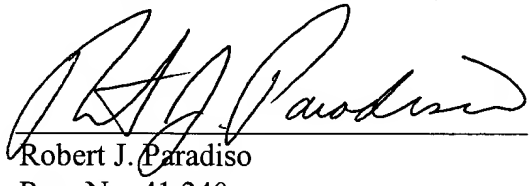
According to currently recommended Patent Office policy the Examiner is requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of

this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By 

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MARKED UP VERSION TO SHOW CHANGES MADE

THE SPECIFICATION HAS BEEN AMENDED AS FOLLOWS:

Page 3, second paragraph

In certain preferred embodiments, the present invention comprises a controlled release dosage form that delivers an opioid agonist and an opioid antagonist over an extended period of time. In these oral embodiments, the dosage form includes an amount of an opioid agonist, preferably a bimodally [biomodally]-acting opioid agonist, and an amount of an opioid antagonist, and upon administration the dosage form delivers an analgesic or sub-analgesic amount of the opioid agonist over the dosing interval, along with an amount of the opioid antagonist effective to enhance the analgesic potency of the opioid agonist and attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the opioid agonist.

Page 3, fourth paragraph

The present invention is also directed to the use of the above-mentioned controlled release formulations for maintenance treatment [treatement] of previously detoxified opiate addicts.

Page 7, second full paragraph

When the controlled release dosage form comprises a transdermal delivery system, the [The] rate of delivery of the opioid agonist will be such that a sufficient mean relative release rate (or flux rate) of the opioid agonist contained in the dosage form is delivered from the transdermal dosage form upon administration. The rate of delivery of the opioid antagonist will be such that an effective amount of the opioid antagonist is delivered to attenuate the anti-analgesia,

hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the opioid agonist during the intended dosing interval. Preferably, rate of delivery of the opioid antagonist will be such that an effective amount of the opioid antagonist is delivered to enhance the analgesic potency of the opioid analgesic during the dosing interval of the controlled release dosage form. It is not necessary that substantially all of the opioid antagonist be delivered from the controlled release dosage form to meet these goals.

Page 8, first full paragraph

The controlled release dosage forms of the present invention preferably deliver the opioid antagonist (e.g., excitatory opioid receptor antagonists) at such a level that the opioid antagonist has selective antagonist action at excitatory, but not inhibitory, opioid receptors. In addition, since the antagonists preferably enhance the analgesic potency of the agonists, the agonists become effective when administered at reduced doses which would otherwise be subanalgesic. It may be possible to achieve an analgesic effect with 10-100 times lower doses of the (bimodally acting) opioid agonists with the excitatory opioid receptor antagonists of the invention than when the opioid agonist is administered alone. This is because the excitatory opioid receptor antagonists may enhance the analgesic effects of the <u>opioid</u> [opoid] agonists by attenuating the anti-analgesic excitatory side effects of the opioid agonists. Therefore, in certain preferred embodiments of the invention, the opioid agonist is included in the dosage form and is delivered in an amount which is less than that which has been typically administered for analgesia. In certain embodiments of the invention, the opioid antagonist is delivered such that the amount of opioid agonist included in the dosage form is, e.g., about 10 to about 100 times less than the amount of that opioid agonist typically dosed over the dosing interval.

Paragraph bridging pages 10 and 11

The excitatory opioid receptor antagonists of the invention are preferably selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine,

pharmaceutically acceptable salts thereof and mixtures thereof.[.] Other opioid antagonists include nalmefene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof. In certain preferred embodiments, the opioid antagonist is naloxone or naltrexone.

Paragraph bridging pages 16 and 17

The controlled release dosage form can be a transdermal patch comprising: (a) a backing layer which is substantially impervious to said opioid agonist and opioid antagonist; and (b) a polymer matrix layer which is adhered to said backing layer and which has dispersed therein said opioid agonist and opioid antagonist, said polymer being bioacceptable and permitting said opioid agonist and opioid antagonist to be transmitted for transdermal absorption, said opioid agonist and opioid antagonist being stable in said polymer matrix.

Page 35, third paragraph

For example, a matrix in addition to the opioid agonist and the opioid antagonist, may include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. Such matrices may also include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit® RSPO - the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material. When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° and 90°C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon. In certain embodiments, the [the]

oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol as part of the controlled release matrix.[.]

THE ABSTRACT HAS BEEN AMENDED AS FOLLOWS:

Controlled-release dosage forms containing an opioid agonist; an opioid antagonist; and a controlled release material release during a dosing interval an analgesic or sub-analgesic amount of the opioid agonist along with an amount of the [said] opioid antagonist effective to attenuate a side effect of the [said] opioid agonist. The dosage form provides analgesia for at least about 8 hours when administered to human patients. In other embodiments, the dose of antagonist released during the dosing interval enhances the analgesic potency of the opioid agonist.

THE CLAIMS HAVE BEEN AMENDED AS FOLLOWS:

37. A transdermal delivery system for an opioid analgesic, comprising an opioid agonist and an opioid antagonist contained in a reservoir or matrix and capable of delivery from the system [device] in a controlled manner, such that when the system [device] is applied to the skin of a human patient, the opioid agonist is delivered at a [an] mean relative release rate effective to provide analgesia to the [said] patient for at least 3 days, and the opioid antagonist is delivered at a mean relative release rate sufficient to reduce a side effect [effects] associated with the opioid agonist, said antagonist selected from the group consisting of naloxone, naltrexone, cyclazacine, levallorphan and pharmaceutically acceptable salts thereof [but not sufficient to negate the analgesic effectiveness of the opioid].

The following new claims have been added.

40. (New) The transdermal delivery system of claim 37, wherein said opioid antagonist comprises naloxone or a pharmaceutically acceptable salt thereof.

41. (New) The transdermal delivery system of claim 37, wherein said opioid antagonist comprises naltrexone or a pharmaceutically acceptable salt thereof.

42. (New) The transdermal delivery system of claim 37, wherein said opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures thereof and pharmaceutically acceptable salts thereof.

43. (New) The transdermal delivery system of claim 42, wherein said opioid agonist comprises fentanyl or a pharmaceutically acceptable salt thereof.

44. (New) The transdermal delivery system of claim 42, wherein said opioid agonist comprises buprenorphine or a pharmaceutically acceptable salt thereof.

45. (New) The transdermal delivery system of claim 42, wherein said opioid agonist comprises morphine or a pharmaceutically acceptable salt thereof.

46. (New) The transdermal delivery system of claim 42, wherein said opioid agonist comprises hydromorphone or a pharmaceutically acceptable salt thereof.

47. (New) The transdermal delivery system of claim 42, wherein said opioid agonist comprises oxycodone or a pharmaceutically acceptable salt thereof.

48. (New) The transdermal delivery system of claim 37, wherein the opioid agonist and the opioid antagonist are released at substantially proportionate rates.

49. (New) The transdermal delivery system of claim 37, wherein the opioid antagonist is treated to modify its release rate before it is combined with the opioid agonist, such that when the opioid agonist and the treated antagonist are combined into the transdermal delivery system, the opioid agonist and antagonist are released from the system at substantially proportionate rates.